REMARKS

1. Preliminary Remarks

Claims 1 to 393 remain pending in this application. Claims 362-369 and 373-376 were rejected in the Office Action of December 22, 2003. Claim 375 was rejected under 35 U.S.C. §112, second paragraph, as indefinite. Claims 362-369, 373-374 and 376 were rejected under 35 U.S.C. §102 as anticipated by Dante et al. U.S. Patent No. 5,856,332 ("Dante '332") or Dante et al. U.S. Patent No. 5,817,665 ("Dante '665"). Claim 375 was rejected under 35 U.S.C. §103 as obvious over Dante '332 or Dante '665 in view of Dante et al. U.S. Patent No. 6,034,091 ("Dante '091"). These three Dante patents are collectively refer to herein as "the Dante references".

Claims 1 to 361, 370 to 372, and 377 to 393 are withdrawn from consideration as being drawn to a nonelected invention. Applicant reserves the right to pursue claims 1 to 361, 370 to 372, and 377 to 393 in one or more divisional or continuation applications. The Examiner additionally requested that Applicant elect a single disclosed species from (1) various non-opioid CNS-active agents and (2) opioid receptor antagonists. Applicant elected (1) an antidepressant and (2) nalmefene, with traverse.

2. Rejection Of Claim 375 Under 35 U.S.C. §112, second paragraph

In the Office Action of December 22, 2003, the Examiner rejected claim 375 under 35 U.S.C. §112, second paragraph, as indefinite. The Examiner stated that claim 375 contains the trademarks/trade names Valium®, Ambien®, and Halcion®. The Examiner stated that these are used to identify/describe diazepam, zolpidem and triazolam, respectively.

Applicant has amended claim 375 so that it recites diazepam, zolpidem and triazolam rather than the trademarks. Applicant submits that this amendment clarifies and does not narrow the claim, since the trademarks have been replaced with generic terms. Applicant requests reconsideration and withdrawal of this rejection.

3. Rejection Of Claims 362-369, 373-374 and 376 Under 35 U.S.C. §102 And Claim 375 Under 35 U.S.C. §103

Claims 362-369, 373-374 and 376 were rejected under 35 U.S.C. §102 as anticipated by Dante '332 or Dante '665. Claim 375 was rejected under 35 U.S.C. §103 as obvious over Dante '332 or Dante '665 in view of Dante '091 (collectively "the Dante references"). Applicant submits that Dante '332 and Dante '665 do not anticipate amended claims 362, 364 and 373 or their dependent claims because Dante '332 and Dante '665 do not suggest or teach compositions comprising amounts of opioid inhibitors of ABC drug transporters or opioid receptor antagonists in the range of 0.0001 µm to 100 µm. Additionally, with respect to claims 364 and 373, Dante '332 and Dante '665 do not suggest or teach that opioid receptor antagonists such as naloxone, naltrexone, and nalmefene are inhibitors of ABC drug transporters. Furthermore, the subject matter of claim 375 is not taught or suggested by Dante '332, Dante '665, or Dante '091, or by any combination of those references.

Claims 362-363 and 373-376 are drawn to compositions comprising a non-opioid CNS active agent and an opioid receptor antagonist, and claims 364-369 are drawn to compositions comprising a non-opioid CNS active agent and an opioid inhibitor of an ABC drug transporter. Applicant has discovered that the opioid receptor antagonists are inhibitors of ABC transporter proteins with unexpected effects, as explained in the specification:

> The present invention is based in part on surprising results from transport studies of drug agents across the blood brain barrier that demonstrates that compounds previously identified as opioid receptor antagonists are inhibitors of ABC drug transporter proteins, including of the P-glycoprotein found at the blood brain barrier, PGP1a. Administration of opioid receptor antagonists, such as naloxone, nalmefene and naltrexone, unexpectedly resulted in increased brain concentrations of co-administered therapeutic agents, such as CNS-active agents. Such antagonists also unexpectedly reduced the efflux and/or increased the influx of the co-administered agents.

(Application, page 6, lines 14-21). Dante '332 and Dante '665 do not disclose suggest or teach that opioid receptor antagonists are ABC drug transporter inhibitors.

Claims 362-369 and 373-376, as amended herein, cannot be anticipated or rendered obvious by the Dante references since they do not teach or suggest compositions comprising an amount in the range of 0.0001 μM to 100 μM of an opioid receptor antagonist. Applicant has disclosed this range in the specification at, for example, page 20, lines 9-11.

The Dante references do not suggest or teach compositions comprising an amount of an opioid receptor antagonist in the range of 0.0001 μM to 100 μM. Instead they teaches the use of 25 mg or 50 mg doses of Trexan® naltrexone. "Preferably, in the present invention, the patient is given a dose of 25 or 50 mg. of Trexan per day in the morning, depending on the size of the patient and the severity of the symptoms of depression." (see, for example, Dante '665, col. 4, lines 33-36). Indeed, if a patient experiences sleepiness from the naltrexone, Dante suggests starting with a lower dose of 10 mg but then increasing to the more desirable 25 mg:

> Some patients may experience several days of sleepiness when Trexan is used in combination with tricyclic or a-typical antidepressants and in these patients an alternative dose would be in the neighborhood of 10 mg taken at bedtime for the first three days of administration. On the fourth day, 10 mg may be administered and assuring that no sleepiness is evident **the dose should be advanced to 25 mg**. each morning for the next four weeks.

(see, for example, Dante '665, col. 4, lines 37-44) (emphasis added). The Dante references do not teach or suggest compositions comprising an amount of an opioid receptor antagonist in the range of 0.0001 micromolar to 100 micromolar. Accordingly the Dante references do not teach or suggest the subject matter of amended claims 362, 364 and 373 or their dependent claims.

Furthermore, amended claims 364 and 373, and their dependent claims relate to compositions comprising (a) a non-opioid CNS-active agent, and (b) **an ABC drug**

transporter protein-inhibiting amount of an opinion inhibitor of an ABC drug transporter (in claim 364) or an opioid receptor antagonist (in claim 373), wherein the amount is in the range of from 0.0001 μM to 100 μM. Applicant has discovered that opioid antagonists such as naloxone, naltrexone, and nalmefene are effective as inhibitors of ABC drug transporter proteins such as P-glycoprotein. Applicant disclosed the inhibition of PGP-mediated transport of digoxin by naloxone, naltrexone, and nalmefene in Tables 1, 2 and 3, respectively of the present specification (pages 20-22 of the application). The Dante references do not suggest or teach that opioid receptor antagonists are inhibitors of ABC drug transporters. Accordingly the Dante references cannot anticipate or render obvious amended claims 364 or 373, or their dependent claims.

4. Correction of Typographical Error

Claim 373 has also been amended to correct an obvious typographical error. Applicant submits that the amendment is clerical in nature and does not narrow the scope of the claim.

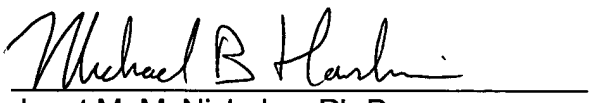
5. Conclusion

For the foregoing reasons, Applicant respectfully submits that the pending claims are not anticipated or rendered obvious by Dante '332 or Dante '665 or Dante '091, or by any combination of them, and that the anticipation and obviousness rejections may properly be withdrawn. Thus, claims 362-369 and 373-376 as amended herein are in condition for allowance.

The Examiner is invited to telephone Applicant's representative to discuss any questions or be of any assistance to the Examiner in the reconsideration and allowance of this case.

Respectfully submitted,

Date: April 22, 2004



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